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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/877,317	06/17/1997	PHILLIP DAN COOK	ISIS-2508	5925

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EXAMINER	
MARTINELL, JAMES	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/877,317	COOK, PHILLIP DAN	
	Examiner	Art Unit	
	James Martinell	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-16,19,20 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-16,19,20 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 May 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The finality of the Office action mailed September 1, 2004 is withdrawn. A new reference, Hyrup et al (Bioorganic & Medicinal Chemistry 4 (1), 5 (1996)), is cited.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 13-16, 19, 20, and 24-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of PNAs (protein nucleic acids) as antisense agents in unicellular organisms and cells in culture, does not reasonably provide enablement for the use of PNAs as antisense agents in multicellular organisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The instant application does not adequately teach an effect on any organism by administration of any of the modified PNAs mentioned in the claims. Rojanasakul (Advanced Drug Delivery Reviews 18: 115 (1996)), Ma et al (Biotechnology Annual Reviews 5: 155 (2000)), Chiarantini et al (Biochemistry 41: 8471 (2002)), and Hyrup et al (Bioorganic & Medicinal Chemistry 4 (1), 5 (1996)) are cited here as evidence that antisense treatment of organisms would have required undue experimentation from one of skill in the art even years after the effective filing date of the instant application. (The earliest possible effective filing date for the instant claims is 1991. Rojanasakul was published in 1996 and reviews literature published as late as 1995, Ma et al was published in 2000 and reviews literature published as late as 1998, Chiarantini et al was published in 2002), and Hyrup et al was published in 1996 and reviews literature published as late as 1995. The Court of Appeals for the Federal Circuit (*In re* Wands, 858 F .2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), recognized no fewer than eight factual considerations to be made in the determination of enablement. They are: (1) the quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. These factual considerations will be taken in turn.

(1) The quantity of experimentation: The quantity of experimentation needed to practice the claimed invention using the instant disclosure would be high. Rojanasakul lists several of the pitfalls and difficulties of getting antisense inhibition in multicellular animals *in vivo* (*i.e.* in living organisms, not in cells in culture, which Rojanasakul refers to as *in vitro* studies (*e.g.*, see page 118, column 1, lines9-13)). Although Rojanasakul is not involved with PNAs *per se*, it is expected that the difficulties of using PNAS would be of similar type and be at least as great as the difficulties of using oligonucleotides and modified oligonucleotides. Experimentation would be needed to establish whether the PNAs were taken up by cells at all and whether they were taken up by cells that are actually producing the offending protein (*e.g.*, see Rojanasakul, page 118, column 1, lines 16-27). More experimentation would be needed to determine the method of action of the PNAs (*e.g.*, claim 19) because even if protein synthesis activity is diminished, it may not be caused by specific hybridization of an antisense agent (*e.g.*, see Rojanasakul at page 118, near the bottom of column 1, "An antisense activity is implicated if the antisense ON inhibits better than the controls. However, frequently the control ONs inhibit as well or better than the antisense ON . . . ."). In addition, the experimentation would need to be the more costly and time consuming *in vivo* experimentation since *in vitro* test results may not translate well to *in vivo* situations. For example, see Rojanasakul at page 118, column 2, near the top of the page, "However, it should be pointed out that the *in vitro* effects of PNAs may not necessarily reflect their *in vivo* effects . . . ." The basis question asked by Rojanasakul (page 118, column 1, first paragraph I section 3) is "'Can the antisense approach work *in vivo*?'" The formulation of the question is significant. The author does not ask what it will take to get antisense to work *in vivo*, but whether it will. In any event, the extent of experimentation needed would be high in this active field. Ma et al notes (Abstract), "many obstacles still exist in the development of this [the use of synthetic oligonucleotides as therapeutics] technology." In addition, Ma et al reports the existence of modified ODNs (oligodeoxynucleotides) (*e.g.*, pages 161-162 and Figure 2), but does not relate any successful

use of a PNA *in vivo* in the extensive section entitled "Therapeutic applications and limitations" (pages 172-186). Chiarantini et al indicates that the use of PNAs *in vivo* is problematic. For example, at page 8471, last full paragraph Chiarantini et al states, "Most studies on the use of PNAs in gene therapy or as antisense have been conducted in cell-free systems . . . ; in fact, PNAs suffer from poor membrane permeability . . . . For this reason, studies regarding cell targeting and the deliver of PNA to tissue need to be improved." Chiarantini et al achieved entry of PNAs into macrophages by loading the PNAs into red blood cells. A method not mentioned or hinted at in the instant application and not reported by Chiarantini et al until more than ten years after the effective filing date of the instant application. Hyrup et al describes PNA-DNA chimeras as only "potentially interesting" years after the effective filing date of the instant claims (*e.g.*, Hyrup et al, page 19, last full paragraph). Were antisense using PNA-DNA chimeras (*e.g.*, se claim 13) as workable as applicant argues as of the effective filing date of the instant claims, one is left to wonder why Hyrup et al were not able to report more substantial progress as of 1995-1996. It is the position of the USPTO that the reason is that no progress in the use of PNA-DNA chimeras as antisense agents had been made, this particular utility being a mere possibility at the time.

(2) The amount of direction or guidance presented: The instant application does not provide any guidance in connection with actual use of the PNAs mentioned in the claims in any multicellular organism *in vivo*. The only locations in the instant application that mention the administration of antisense agents are: (a) Abstract (page 58), (b) Background (pages 2-5), (c) Objects of the Invention (page 5), (d) Brief Description of the Invention (page 8, line 25 through page 9, line 21 and pages 22-23), and (e) Example 17 (pages 41-48). These parts of the instant application describe the administration of antisense agents to organisms in only the most general terms and disclose no particular results.

(3) The presence or absence of working examples: There are no working examples of administration of a PNA antisense agent to a multicellular organism in the instant application.

(4) The nature of the invention: The technical mature of the invention is complex. The synthesis of the PNAs is tedious and tie consuming as are the *in vivo* tests. The interactions of antisense agents and their subjects is complex as evidenced by each one of Rojanasakul, Ma et al, Chiarantini et al, and Hyrup et al in which there is much discussion of possible mechanisms of action as well as possible difficulties with uptake, toxicity, and degradation.

(5) The state of the prior art: The state of the prior art is not clear since there is no prior art of record involving the use of PNAs as antisense agents. Thus, it is only possible to judge the use of PNAs as antisense agents in light of the state of the prior art of using oligonucleotides as antisense agents. This is represented by the review article by Rojanasakul. Hyrup et al does review the PNA literature as of 1995-1996 and report only that the use of PNA-DNA chimeras as antisense agents is "potentially interesting" (*e.g.*, page 19, last full paragraph).

(6) The relative skill of those in the art: The level of those of skill in the art is high. Those of skill in this art most likely have a Ph.D. degree in a chemical or biological laboratory science and some years of post-doctoral experience and who publish their results in refereed journals. The articles by Rojanasakul, Ma et al, Chiarantini et al, and Hyrup et al review 416 papers published between 1951 and 2000 by those who can be considered of skill in this art.

(7) The predictability or unpredictability of the art: The predictability of the art is low since there are no data regarding the use of PNAs as antisense agents and because of the difficulties outlined in Rojanasakul, Ma et al, Chiarantini et al, and Hyrup et al as referred to hereinabove. Even though Rojanasakul indicates that "several ON drugs have already demonstrated enough promise to justify clinical trial" (page 126, last paragraph), this statement does not tell the reader when those clinical trials were started, if at all (only that they have been justified), nor is there an indication of the results. In addition, the statement was made some 3 years after the effective filing date of the instant application. Thus, it is not clear how much this statement can be relied upon to support the notion of enablement, especially in view of the statements in Rojanasakul just prior to that in which the author expresses "good reason for

enthusiastic hope" for the use of ONs as *in vivo* antisense agents. Finally, as mentioned above, Rojanasakul is necessarily limited to discussion of ONs and not PNAs as antisense agents. There is o report in Ma et al of PNAs working *in vivo* even in the long section devoted to the use of ODNs and modified ODNs *in vivo* (pages 172-186), and this nearly a decade after the effective filing date of the instant application. It is presumed that P.D. Cook of Isis Pharmaceuticals, Carlsbad, CA, a co-author of Ma et al, is the same P.D. Cook who is the inventor of the instant application. It is recognized that progress may be rapid in the sciences (*e.g.*, see Enzo Biochem., Inc. v. Calgene, Inc., 188 F .3d 1362, 52 USPQ2d 1129 (Fed. Cir. 1999)) and that what is unpredictable may later become predictable. However, the current record contains no evidence that any of the claimed methods has worked even since the effective filing date of the claims. Since more than a decade has elapsed since the effective filing date of the claims, one might expect that such evidence (published or not) would be readily available to applicants. Applicants are invited to submit any such evidence into this record prior to a final Office action.

(8) The breadth of the claims: The claims are broad because they embrace the use of any PNA as an antisense agent in virtually any organism.

Although claims 20 and 24-26 do not explicitly recite a hybridization step, it is clear from the disclosure as a whole that these claims are construed as requiring hybridization of the PNA antisense agent(s) to nucleic acids within cells of the organism(s) treated in order to achieve any result at all in the claimed treatment methods because no other mechanism of action is disclosed or referred to for the PNAs in the application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Martinell whose telephone number is (571) 272-0719. The fax phone number for Examiner Martinell's desktop workstation is (571) 273-0719. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be e-

mailed to james.martinell@uspto.gov. Since e-mail communications may not be secure, it is suggested that information in such requests be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-0722.

FAX NUMBER

The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. Any Official Communication to the USPTO should be faxed to this number.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

James Martinell, Ph.D.
Primary Examiner
Art Unit 1631

12/11/04